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Water-soluble metal complexes and catalysts Part XI. Novel ligands from tris(hydroxymethyl)phosphane and amino acids: Synthesis and catalytic studies in two-phase hydroformylation☆

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Abstract

Novel water-soluble ligands were prepared in high yields by condensation of various amino acids with tris(hydroxymethyl)phosphane. Rhodium complexes of these ligands, formed in situ, were tested in two-phase hydroformylation of propylene. Selectivity observed with these ligand systems is easily controlled by altering the pH of the reaction mixture.

Keywords: Two-phase hydroformylation; Rhodium catalysts; Amino acids

1. Introduction

Aqueous/organic biphasic systems have attracted huge interest in catalytic reactions by transition metal complexes [1,2]. Biphasic systems have benefits in catalyst separation and recycling. Reduction or complete elimination of organic solvents is also highly advantageous for the development of economical and environmentally friendly processes. The key for such biphasic catalysis is the use of water-soluble phosphines as ligands. Since the launch of the commercial propylene hydroformylation process by Ruhrchemie/Rhône-Poulenc, sulfonated phosphine ligands such as TPPTS (**1**), BISBIS (**2**) and BINAS (**3**) have been widely used as ligands in hydroformylation, hydrogenation and related reactions catalyzed by transition metals (Fig. 1) [3,4].

Preparation of such sulfonated ligands however suffers several significant drawbacks. The use of highly corrosive oleum not only complicates the handling of the reaction mixtures, but also leads to partial oxidation of phosphines. Sodium sulfite which is formed in this reaction is a common impurity in resulting aldehydes and is a source of poisoning of hydrogenation catalysts in the subsequent production of alcohols [5].

Phosphine ligands can also be converted into water-soluble derivatives by the introduction of other polar groups, such as carboxylate, ammonium, phosphonium and hydroxyl groups [6,7]. Amino acids however have received much less attention as possible hydrophilic substituents.

In recent papers by Katti and coworkers, two ligands derived from tris(hydroxymethyl)phosphine (THMP), glycine and alanine were described, and even successfully used in the treatment of copper overload in men [8,9]. Despite obvious possible advantages in two-phase catalysis, e.g. avoidance of corrosive oleum, absence of undesired oxidation, etc., no such work was published up to date in literature.

We decided to synthesize several new water-soluble phosphorous functionalized trimeric amino acids of this ligand family and study their behavior in hydroformylation, aiming to develop efficient rhodium catalytic systems based on these low-cost, easily prepared and environmentally friendly ligands. Propylene has been chosen as a model molecule, as it is of huge importance in modern industrial practices. In this paper we report on synthesis of novel amino acid-conjugated phosphines by a single step condensation of amino acids with

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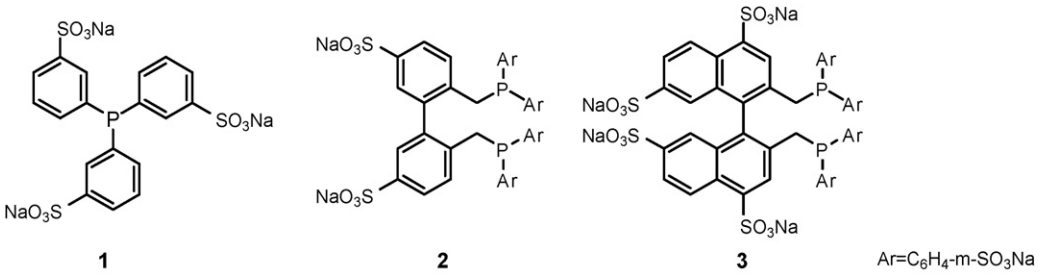


Fig. 1. TPPTS (**1**), BISBIS (**2**) and BINAS (**3**).

tris(hydroxymethyl)phosphine and catalytic behavior of their rhodium complexes in aqueous–organic biphasic hydroformylation of propylene.

2. Experimental section

2.1. General methods

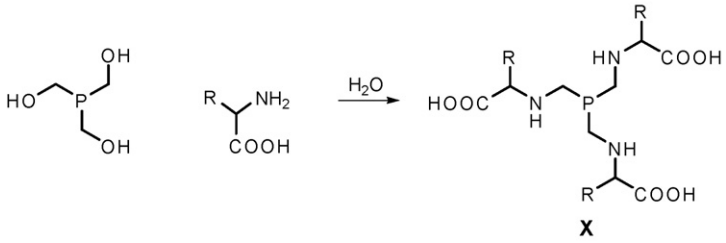
Tris(hydroxymethyl)phosphine (THMP,**4**), [({bis[(carboxymethylamino)methyl]-phosphanyl}methyl)amino]acetic acid [THMP–glycine] (**5**) and 2-[({bis[(1-carboxyethylamino)-methyl]phosphanyl}methyl)amino]propionic acid [THMP–alanine] (**6**) were prepared according to literature procedures [8,9]. All other materials were obtained commercially and were used as received, except as noted. All syntheses were performed under the atmosphere of nitrogen, using solvents dried on an alumina-based solvent purification system. NMR spectra were recorded on a JEOL JMX-GX 400 spectrometer operating at 400 MHz (^{1}H NMR), 100 MHz (^{13}C NMR) and 161 MHz (^{31}P NMR) at room temperature. Chemical shifts are given in ppm. The spectra are calibrated to the residual protons of the solvents or 85% H_3PO_4, as an external standard (^{31}P). NMR multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal. MS spectra were measured at the TU München Mass Spectrometry Laboratory on a Finnigan MAT 90 mass spectrometer using the CI or FAB technique. Elemental analyses were carried out by the Microanalytical Laboratory at the TU München.

3. 2-[({Bis[(1-carboxy-2-phenyethylamino)methyl] phosphanyl}methyl)amino]-3-phenylpropionic acid [THMP–phenylalanine] (7)

THMP (1.00 g, 8.06 mmol) in 10 ml of degassed water was added dropwise to a stirred solution of phenylalanine (4.00 g, 24.2 mmol) in water (250 ml). Colourless solid which separates upon stirring reaction mixture for 24 h at room temperature was filtered off, washed with dry methanol and dried in vacuo. Yield 3.28 g, 72%, mp. 198–199 °C (decomp.). ^{1}H NMR (D_2O): δ 7.45–7.07 (15H, m); 3.88 (3H, t, J = 7.1 Hz); 3.38 (3H, m); 2.82 (9H, m). ^{13}C NMR (D_2O): δ 181.24, 138.90, 129.72, 128.99, 126.99, 67.34 (d, J = 8.4 Hz), 42.56 (d, J = 45.7 Hz), 39.35 (d, J = 10.7 Hz). ^{31}P NMR (D_2O): δ-31.67. Anal. Calcd for $C_{30}H_{36}N_3O_6P$ (565.59): C, 63.71; H, 6.42; N, 7.43. Found C, 63.34; H, 6.09; N, 7.02. IR ν_{max} (KBr)/cm^{-1} 1595, 1552, 1385, 1302, 1018, 746, 698. m/z 433.2 (3%, M^+-3CO_2), 294.0 (42%), 282.0 (92%), 235.0 (100%).

4. 2-[({Bis[(1-carboxy-3-methylbutylamino)methyl] phosphanyl}methyl)amino]-4-methylpentanoic acid [THMP–leucine] (8)

THMP (1.00 g, 8.06 mmol) in 10 ml of degassed water was added dropwise to a stirred solution of leucine (3.17 g, 24.2 mmol) in water (200 ml). Colourless solid which separates upon stirring reaction mixture for 24 h at room temperature was filtered off, washed with dry methanol and dried in vacuo. Yield



X	R	Yield, %
5	-H	93
6	-CH_3	89
7	-CH_2Ph	72
8	-CH_2*i*Pr	69
9	-CH(CH_3)Et	62
10	-*i*Pr	79
11	-$CH_2CH_2CH_2$-	69
12	-CH_2OH	58

Scheme 1. Synthesis of phosphorous functionalized trimeric amino acids.

2.58 g, 69%, mp. 217–218 °C (decomp.). ^{1}H NMR (D_2O): δ 4.14–3.98 (3H, m); 3.17–3.15 (3H, m); 2.83 (6H, td, J = 12 Hz, J = 42 Hz); 1.56–1.40 (9H, m); 0.89 (18H, d, J = 5.2 Hz). ^{13}C NMR (D_2O): δ 182.98, 64.67 (d, J = 35.9 Hz), 59.79 (d, J = 42.1 Hz), 42.82 (d, J = 6.9 Hz), 25.14, 22.53 (d, J = 47.5 Hz). ^{31}P NMR (D_2O): δ-31.05. Anal. Calcd for $C_{21}H_{42}N_3O_6P$ (463.5): C, 54.41; H, 9.13; N, 9.06. Found C, 54.11; H, 8.82; N, 8.69. IR ν_{max} (KBr)/cm^{-1} 3291, 2955, 1598, 1559, 1386, 1018, 839, 673, 512. *m/z* 375.3 (5%, M^+-2CO_2), 213.0 (27%), 201.1 (100%), 156.1 (26%).

5. 2-[({Bis[(1-carboxy-2-methylbutylamino)methyl] phosphanyl}methyl)amino]-3-methylpentanoic acid [THMP–isoleucine] (9)

THMP (1.00 g, 8.06 mmol) in 10 ml of degassed water was added dropwise to a stirred solution of isoleucine (3.17 g, 24.2 mmol) in water (100 ml). Colourless solid which separates upon stirring reaction mixture for 24 h at room temperature was filtered off, washed with dry methanol and dried in vacuo. Yield 2.33 g, 62%, mp. 179–180 °C. ^{1}H NMR (D_2O): δ 4.19–4.11 (3H, m); 3.70–3.65 (3H, m); 3.58–3.43 (3H, m); 2.04–1.91 (3H, m); 1.59–1.44 (3H, m); 1.35–1.21 (3H, m); 1.01–0.92 (24H, m). ^{13}C NMR (D_2O): δ 172.69, 69.09 (d, J = 18.3 Hz), 43.67 (d, J = 17.6 Hz), 36.24 (d, J = 37.5 Hz), 25.84 (d, J = 8.4 Hz), 14.68 (d, J = 32.1 Hz), 11.31 (d, J = 7.7 Hz). ^{31}P NMR (D_2O): δ-35.67. Anal. Calcd for $C_{21}H_{42}N_3O_6P$ (463.5): C, 54.41; H, 9.13; N, 9.06. Found C, 54.02; H, 8.71; N, 8.71. IR ν_{max} (KBr)/cm^{-1} 2976, 1611, 1515, 1394, 1137, 1028, 554. *m/z* 331.3 (14%, M^+-3CO_2), 277.0 (33%), 214.1 (39%), 200.1 (100%), 156.1 (80%).

6. 2-[({Bis[(1-carboxy-2-methylpropylamino)methyl] phosphanyl}methyl)amino]-3-methylbutyric acid [THMP–valine] (10)

THMP (1.00 g, 8.06 mmol) in 10 ml of degassed water was added dropwise to a stirred solution of valine (2.83 g, 24.2 mmol) in water (20 ml). The reaction mixture was stirred under nitrogen for 1 h at room temperature. The solvent was removed in vacuo to obtain a colourless solid which was washed two times with 10 ml of dry methanol and dried in vacuo. Yield 2.68 g, 79%, mp. 162–163 °C. ^{1}H NMR (D_2O): δ 3.07–3.96 (3H, m); 3.07–2.67 (9H, m); 1.86–1.72 (3H, m); 0.97–0.81 (18H, m). ^{13}C NMR (D_2O): δ 181.83, 75.50, 58.98 (d, J = 73.4 Hz), 31.16, 19.17 (d, J = 15.3 Hz). ^{31}P NMR (D_2O): δ-32.10. Anal. Calcd for $C_{18}H_{36}N_3O_6P$ (421.5): C, 51.30; H, 8.61; N, 9.97. Found C, 50.93; H, 8.27; N, 9.59. IR ν_{max} (KBr)/cm^{-1} 1628, 1568, 1474, 1391, 1322, 1034, 816, 772, 681, 555. *m/z* 228.1 (3%), 186.1 (38%), 172.1 (100%), 132.0 (49%).

7. Tris([pyrrolidine-2-carboxylic acid-1-yl]methyl) phosphine [THMP–proline] (11)

THMP (1.00 g, 8.06 mmol) in 10 ml of degassed water was added dropwise to a stirred solution of proline (2.78 g, 24.2 mmol) in water (50 ml). The reaction mixture was stirred under nitrogen for 2 h at room temperature. The reaction mixture was concentrated in vacuo to about 10 ml. Upon addition of methanol (40 ml) colourless oil separated and was dried in vacuo to obtain the title compound. Yield 1.83 g, 69%. ^{1}H NMR (D_2O): δ 4.17–4.10 (3H, m); 3.99–3.87 (3H, m); 3.83–3.71 (6H, m); 3.31 (3H, apparent q, J = 9.6 Hz); 2.61–2.49 (3H, m); 2.31–1.95 (9H, m). ^{13}C NMR (D_2O): δ 173.96, 70.64, 58.10, 52.32 (d, J = 13 Hz), 29.01, 23.41. ^{31}P NMR (D_2O): δ-31.49. Anal. Calcd for $C_{18}H_{30}N_3O_6P$ (415.4): C, 52.04; H, 7.28; N, 10.12. Found C, 51.72; H, 6.89; N, 9.68. IR ν_{max} (KBr)/cm^{-1} 1631, 1401, 1321, 1040, 768, 570. *m/z* 320.9 (5%), 130.0 (93%), 102.0 (100%).

8. 2-[({Bis[(1-carboxy-2-hydroxyethylamino)methyl] phosphanyl}methyl)amino]-3-hydroxypropionic acid [THMP–serine] (12)

THMP (1.00 g, 8.06 mmol) in 10 ml of degassed water was added dropwise to a stirred solution of serine (2.54 g, 24.2 mmol) in water (50 ml). The reaction mixture was stirred under nitrogen for 2 h at room temperature. The reaction mixture was concentrated in vacuo to about 10 ml. Upon addition of methanol (40 ml) colourless oil separated and was dried in vacuo to obtain the title compound. Yield 1.82 g, 58%. ^{1}H NMR (D_2O): δ 4.21–4.10 (3H, m); 4.03–3.92 (6H, m); 3.84 (3H, br); 3.71–3.47 (6H, m). ^{13}C NMR (D_2O): δ 171.51, 65.38, 59.45, 44.11 (d, J = 13 Hz). ^{31}P NMR (D_2O): δ-41.08. Anal. Calcd for $C_{12}H_{24}N_3O_9P$ (385.3): C, 37.41; H, 6.28; N, 10.91. Found C, 37.09; H, 6.65; N, 10.59. IR ν_{max} (KBr)/cm^{-1} 1631, 1384, 1086, 1021, 562. *m/z* 253.1 (100%, M^+-3CO_2), 177.0 (34%), 163.0 (86%), 137.0 (78%).

9. Hydroformylation

Rhodium acetate (36.8 mg, 0.083 mmol) was dissolved in water (40 ml) and toluene (20 ml) under nitrogen. The corresponding ligand was added in one portion. Internal standard (hexane, 1.00 g, 116 mol) was added via a syringe. The pH of the aqueous phase was set with hydrochloric acid or sodium hydroxide. The resulting mixture was transferred to a Parr autoclave (300 ml, 4591) via a syringe under nitrogen. The autoclave was flushed with propylene for two times. The reaction vessel was then once more pressurized with propylene and heated up to the set temperature. Initial pressure of 1:1 mixture of hydrogen and carbon monoxide was set at 100 bar. The reaction mixture was rigorously mechanically stirred for 5 h. The stirring rate was kept constant for all experiments. During this time samples were taken, and after phase separation, organic phase was subjected to GC analysis.

10. Results and discussion

10.1. Synthesis of the ligands

Phosphorous functionalized trimeric amino acids were prepared by the addition of tris(hydroxylmethyl)phosphine to a threefold excess of corresponding amino acid, via Mannich-type condensation reaction in water in 60–90% yields (scheme 1 scheme 1).

Table 1
Effect of the temperature on the biphasic hydroformylation of propylene[a]

Temperature (°C)	Conversion (%)	l/b	TOF (h^{-1})[b]
80	44	1.47	88
100	83	1.43	166
120	93	1.39	186

[a] Reaction conditions: $P = 100$ atm ($CO:H_2 = 1$); propylene 166 mmol; S/Rh = 1000 (molar ratio); THMP–glycine/Rh = 5 (molar ratio); time, 5.0 h.
[b] Average turnover frequency: TOF (h^{-1}) = h^{-1} × mol (aldehyde)/mol (rhodium).

Compounds **5**–**10** are colourless crystalline air-stable substances, whereas **11** and **12** are colourless highly viscous oils. They are soluble in water and nearly completely insoluble even in polar organic solvents such as alcohols or acetone. The $^{31}P\{^1H\}$ NMR spectra of these compounds showed sharp singlets between −31 and −41 ppm. ^1H and ^{13}C NMR spectra are also consistent with those of the proposed structures.

10.2. Hydroformylation of propylene catalyzed by Rh/THMP–amino acids

The aqueous–organic biphasic hydroformylation of propylene was carried out using Rh/THMP–amino acids as the catalysts, which were prepared in situ from rhodium acetate and corresponding THMP–amino acid. The effects of the temperature, the molar ratio of THMP–amino acids to rhodium and pH-value of the aqueous phase were investigated.

The effect of temperature on propylene hydroformylation was investigated with THMP–glycine (**5**) at the isoelectric point of the ligand and is shown in Table 1. Under the used conditions, conversion of propylene increases with increasing temperature. However the ratio of linear to branched aldehyde (l/b) decreases as the temperature increases.

Table 2 shows the results of propylene hydroformylation with various molar ratios of ligand to rhodium (THMP–glycine/Rh). As can be seen from it, the activity of the catalyst is not strongly affected by the change of the ligand/rhodium ratio. However, the l/b ratio improves sharply while the THMP–glycine/Rh ratio increases from 1 to 5. Further increase does not improve the l/b value. It is indicative that complete saturation and stable coordination of phosphine ligand at the metal center occurs at this ligand/Rh ratio.

Because of the usage of amino acids as building blocks for our new catalysts, we have anticipated, that pH-change in the proximity of the isoelectric point will have a distinctive effect on the catalytic properties of these ligands. We have therefore determined isoelectric points for all ligands by means of simple acid–base titrations. This data is summarized in Table 3.

Table 2
Effect of THMP–glycine/Rh (molar ratio) on the biphasic hydroformylation of propylene[a]

THMP–glycine/Rh (molar ratio)	Conversion (%)	l/b	TOF (h^{-1})
1	97	0.88	194
2	95	1.09	190
5	93	1.39	186
10	92	1.43	184

[a] $T = 120$ °C; all other conditions are the same as in Table 1.

Table 3
Isoelectric points of THMP–amino acid conjugates

Ligand	p*I*
5	6.78
6	6.76
7	6.31
8	6.64
9	6.72
10	6.81
11	7.01
12	5.89

To find out the effect of H^+ concentration on the hydroformylation of propylene, we have tested all the ligands at their isoelectric points as well as at lower and higher pH-values. The effect of pH is shown in Fig. 2. It was found that the l/b ratio increases with the decrease in pH. It can be explained by the change of the electronic properties of the ligands. At lower pH, the amino group is protonated and therefore positively charged. This decreases the donating ability of the ligand and therefore leads to less stable rhodium–CO bond in catalytically active complex. In the course of the reaction, CO will dissociate, and because of their steric demand, the remaining ligands will direct the selectivity toward the linear aldehyde [10]. The best results within this ligand series were achieved with THMP–proline (**11**) which is probably due to additional steric hindrance caused by the bulky pyrrolidine ring in the direct proximity of phosphorous.

The same pH dependence was also observed for the conversion of propylene, as shown in Fig. 3. In this case, however, the best results were achieved not with proline, but with phenylalanine. One of the possible explanations for this fact could be the more electronegative nature of the phenyl group, leading to the less basic ligand. This in turn, for the above-mentioned reasons, leads to the easier formation of active species and more active catalyst. The studies of metal coordination of these ligands to rhodium and iridium are currently underway in our laboratory and will be published elsewhere soon.

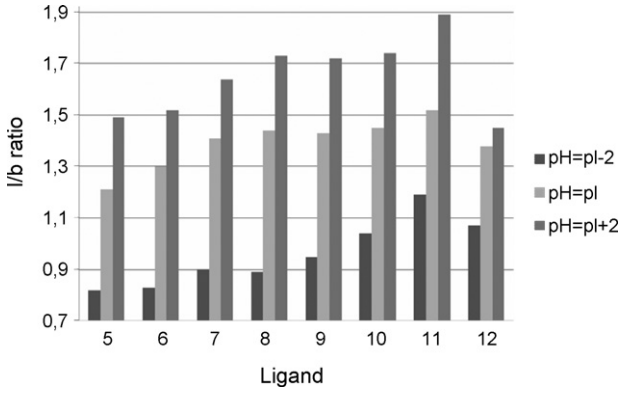


Fig. 2. Dependence of l/b ratio in hydroformylation of propylene on pH of the reaction mixture. Reaction conditions $T = 120$ °C; L/Rh = 10 (molar ratio); time, 3 h; all other conditions are the same as in Table 1.

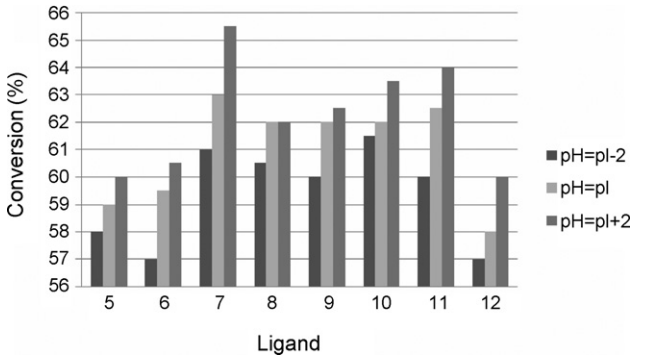


Fig. 3. Dependence of conversion in hydroformylation of propylene on pH of the reaction mixture. Reaction conditions are the same as in Fig. 2.

Table 4
Hydroformylation of propylene: recycling experiments[a]

Run	Conversion (%)	l/b
1	92	1.43
2	76	1.12
3	52	1.02

[a] $T = 120\,^{\circ}C$; L/Rh = 10 (molar ratio); all other conditions are the same as in Table 1.

In all catalytic hydroformylation reactions, the products were recovered from the toluene layer, and the catalyst was present in the water layer. In order to test the catalyst stability three catalytic runs were performed, by recycling the same water layer containing THMP–glycine (**5**) as a model ligand. However, significant decrease in the activity and selectivity was observed, as shown in Table 4. Studies of the decomposition pathways of these new ligands are currently underway in our laboratory.

11. Conclusion

New water-soluble ligands derived from tris(hydroxymethyl)phosphane and amino acids were synthesized by a straightforward Mannich-type condensation in water. They exhibit catalytic activity in two-phase hydroformylation of propylene. Selectivity of these ligands can be regulated by pH-change of the reaction mixture.

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